Interaction between Environmental Pollutants and Respiratory Infections

by Richard Ehrlich*

The major aspects that must be considered in studies of the health effects of environmental pollutants are: the direct damage due to the exposure, the role of a pre-existing disease, and effects of the exposure on the response to secondary stresses. In experimental studies at concentrations of air pollutants found in urban environments frank toxicological responses are rarely observed. However, exposure to a secondary stress, i.e. respiratory challenge with infectious bacteria, can exacerbate the response of the experimental host.

Changes in the resistance to respiratory infections provide a highly sensitive experimental animal model system, which is increasingly used in studies of health effects of air pollutants. This model indicates the impairment of the basic defense mechanisms of the respiratory system by the combined exposure to low concentrations of pollutants and the superimposed bacterial infection.

Changes in the resistance to respiratory infections were studied in various species of laboratory animals. *S. pyogenes* and *K. pneumoniae* are the bacteria of choice to induce the pulmonary infection. Included in the studies are short-term single and multiple exposures as well as long-term exposures to gaseous pollutants such as O_3 and NO_2 and particulate pollutants such as sulfates and nitrates. Changes in the resistance are measured as excess mortalities and reduced survival time as compared to those in infected animals not exposed to the pollutants. Other parameters measured ranged from changes in the immune response to changes in retention rates of bacteria in lungs.

Introduction

Several papers presented at this symposium have dealt with the mechanisms which are active in protecting the respiratory tract against damage due to inhalation of airborne contaminants. The mechanisms include the mucociliary system, phagocytic activity of alveolar macrophages, and the immunity of the respiratory tract. These mechanisms are indeed the same which play a significant role in protecting a host against respiratory infections. Thus, the effects of air pollutants on the respiratory tract are of special importance in relation to respiratory infections.

Health effects studies of air pollutants have been usually concerned with the causal association between a single pollutant and a disease state. However, it is well known that frequently more than one factor is responsible for the occurrence of natural diseases. Therefore, multiple causalities must be considered in the assessment of biological effects of air pollutants. One such interaction is depicted by

the animal model system which reflects the exacerbation of bacterial respiratory infections by inhalation of air pollutants. Indeed, changes in the resistance to respiratory infections provide a highly sensitive experimental model which is with increasing frequency used in studies of health effects of air pollutants.

The relationship between exposure to air pollutants and the resistance to respiratory infections has been investigated in our laboratories since 1955. The gaseous pollutants included in these studies were ozone, nitrogen dioxide, sulfur dioxide, and peroxyacetyl nitrate. Particulate pollutants included sulfuric acid, various sulfates and nitrates, and oxides of platinum, palladium, manganese, and nickel. The studies were designed to determine the effects of single and multiple exposures to a single pollutant or to pollutant mixtures.

Materials and Methods

The experimental protocol used in the studies calls for exposure of a group of animals, usually 6 to 8-week old mice, to a pollutant and another group to

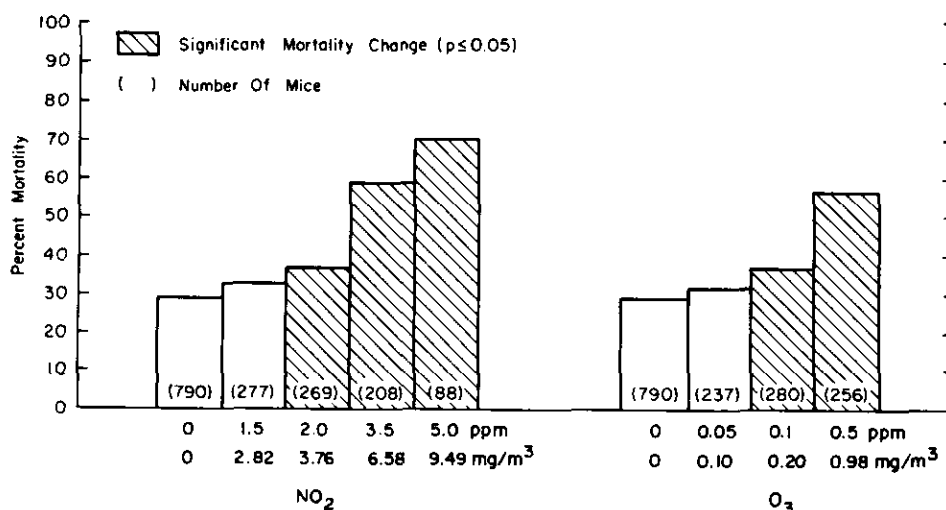*Life Sciences Research, IIT Research Institute, 10 West 35th St., Chicago, Illinois 60616.

Figure 1. Mortality rates in mice exposed for 3 hr to O₃ or NO₂ and challenged with Streptococcus aerosol (2).

clean air. After the exposure the two groups of mice are combined and within less than 1 hr challenged by the respiratory route with an aerosol of the infectious bacteria, either *Streptococcus pyogenes* or *Klebsiella pneumoniae*. The challenge usually lasts for 10 to 15 min and results in the deposition of approximately 750 to 1500 viable bacteria per lung. After the challenge the mice are kept in an isolated clean-air room for 14 days observation period. The changes in resistance to the infection are usually measured by two parameters, namely, changes in mortality rates and in survival time when compared to those seen in infected mice exposed to filtered air. In addition to mortality and survival, several other parameters are measured. They include clearance rate of inhaled viable bacteria from the lungs, damage to the respiratory tract tissue as observed by conventional histopathological and scanning electron microscopic examination, development of lung edema, activity and function of alveolar macrophages, humoral and cell-mediated immune responses and various clinical pathology measurements. To determine the statistical significance of the differences in responses between animals exposed to the pollutants and those exposed to clean air the chi-square analysis, Student's *t*-test, analysis of variance and linear regression analysis were used, as appropriate.

The details of experimental methods used for preparation of the environmental atmospheres, monitoring of the pollutants, infectious challenge with the bacterial aerosols and the assay of the various health parameters were described in previous publications (*1-3*).

Results

Effects of Gaseous Pollutants

Figure 1 shows mortalities resulting from a single 3-hr exposure of mice to either nitrogen dioxide or ozone and challenge with Streptococcus aerosol (2). Statistically significant increases ($p \le 0.05$) in actual mortality are seen after the single exposure to either 3.76 mg/m³ NO_2 or 0.2 mg/m³ O_3. These data indicated the high sensitivity of this assay system, whereby a significant physiological response can be attained at concentrations of air pollutants frequently found in urban environments. The mortality rates of mice exposed to ozone are in a close agreement with those reported by Coffin et al. (*4*). In his work the death rate in control mice was 10.6%, in those exposed to 0.14 mg/m³ O_3 20.0%, to 0.2 mg/m³ O_3 35.0 and to 0.98 mg/m³ O_3 80.0%. Thus the reproducibility of this animal model system among two different laboratories and during two different time periods is apparent.

In an urban environment the concentrations of air pollutants vary considerably with their rate of emission and meteorological conditions. This frequently results in presence of low baseline concentrations of a pollutant with superimposed short-duration peaks of higher concentration of the same pollutant. For example, a large portion of nitrogen oxides present in urban environment is generated by the vehicular traffic. Morning rush hour traffic results in high concentrations of nitric oxide and hydrocarbons which in presence of sunlight are converted to nitrogen
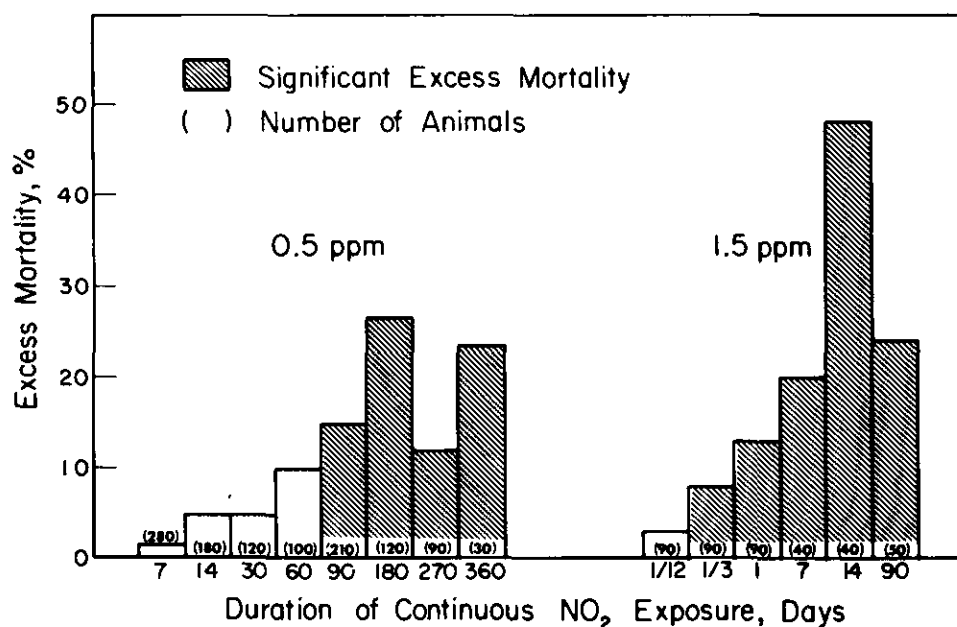
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FIGURE 2. Excess mortalities in Swiss albino mice after chronic exposures to 0.5 ppm and 1.5 ppm NO₂ and challenged with *K. pneumoniae* (5).

dioxide. Subsequent sunlight irradiation of nitrogen dioxide results in increase in concentrations of ozone. Human populations therefore can be exposed over extended periods of time to low concentrations of NO₂ or to low concentrations of this pollutant with superimposed peaks of elevated concentrations of NO₂ and O₃ mixtures.

Figure 2 shows the effects of continuous 24 hr/day, 7 day/week exposure to 0.94 mg/m³ (0.5 ppm) or 2.82 mg/m³ (1.5 ppm) NO₂ on the susceptibility to *K. pneumoniae* infection (5). The increased mortality rates in mice exposed to 0.94 mg/m³ NO₂ for 3 months or longer, and to 2.82 mg/m³ NO₂ for 8 hr or longer were significant (p ≤ 0.05). Excess mortality was also present in mice exposed to nitrogen dioxide for the shorter time periods, but the differences were not statistically significant.

To determine the effects of inhalation of nitrogen dioxide and ozone mixtures, groups of mice were exposed for 3 hr to various concentrations of each pollutant, a mixture containing the same concentration of the two pollutants or to filtered air. The four groups were then simultaneously challenged with Streptococcus aerosol. The differences between mortality among mice exposed to the pollutants and the corresponding control mice, challenged with the bacterial aerosol but exposed to filtered air are shown in Table 1 (2). The data indicate that the effects of the 3-hr exposure to the NO₂ and O₃ mixture were additive. In most instances the excess mortalities were equivalent or somewhat higher than the sum induced by exposure to each individual pollutant.

To further simulate the realistic condition of urban

Table 1. Actual and expected changes in mortality in mice exposed for 3 hr to nitrogen dioxide and ozone mixtures and challenged with Streptococcus aerosol.

NO₂ concentration		No O₃	Mortality change at various O₃ concentrations, %[a]					
			0.05 ppm O₃ (0.10 mg/m³)		0.1 ppm O₃ (0.20 mg/m³)		0.5 ppm O₃ (0.98 mg/m³)	
ppm	mg/m³	A	A	E	A	E	A	E
0	0	0	5.4		7.2		28.6[b]	
1.5	2.82	−1.7	4.6	3.7	4.2	5.5	23.9[b]	26.9
2.0	3.76	14.3[b]	22.0[b]	19.7	—	21.5	56.2[b]	42.9
3.5	6.58	28.2[b]	—	33.6	38.5[b]	35.4	68.7[b]	56.8
5.0	9.40	35.7[b]	—	41.1	—	42.9	65.3[b]	64.3

[a]Pollutant mortality — control mortality; A = actual mortality change; E = expected mortality change.
[b]Significant change in mortality compared to infected mice exposed to filtered air (p ≤ 0.05).

population exposure, groups of mice were exposed continuously 24 hr/day (7 day/week) to a background concentration of 0.19 mg/m³ NO_2 with superimposed 3-hr daily peaks (5 days/week) of either 0.94 mg/m³ NO_2 or a mixture consisting of 0.94 mg/m³ NO_2 and 0.20 mg/m³ O_3. Inasmuch as under true environmental conditions exposure to the pollutants can be expected also to occur after the

inhalation of the infectious bacteria, groups of mice were exposed to the pollutants before and for the 14-day period following the infectious challenge. Results shown in Figure 3 indicate that the combination of extended exposure to the pollutants and continuation of the exposure after the respiratory challenge with Streptococcus aerosol was most deleterious. Upon such an exposure sequence increased mortal-
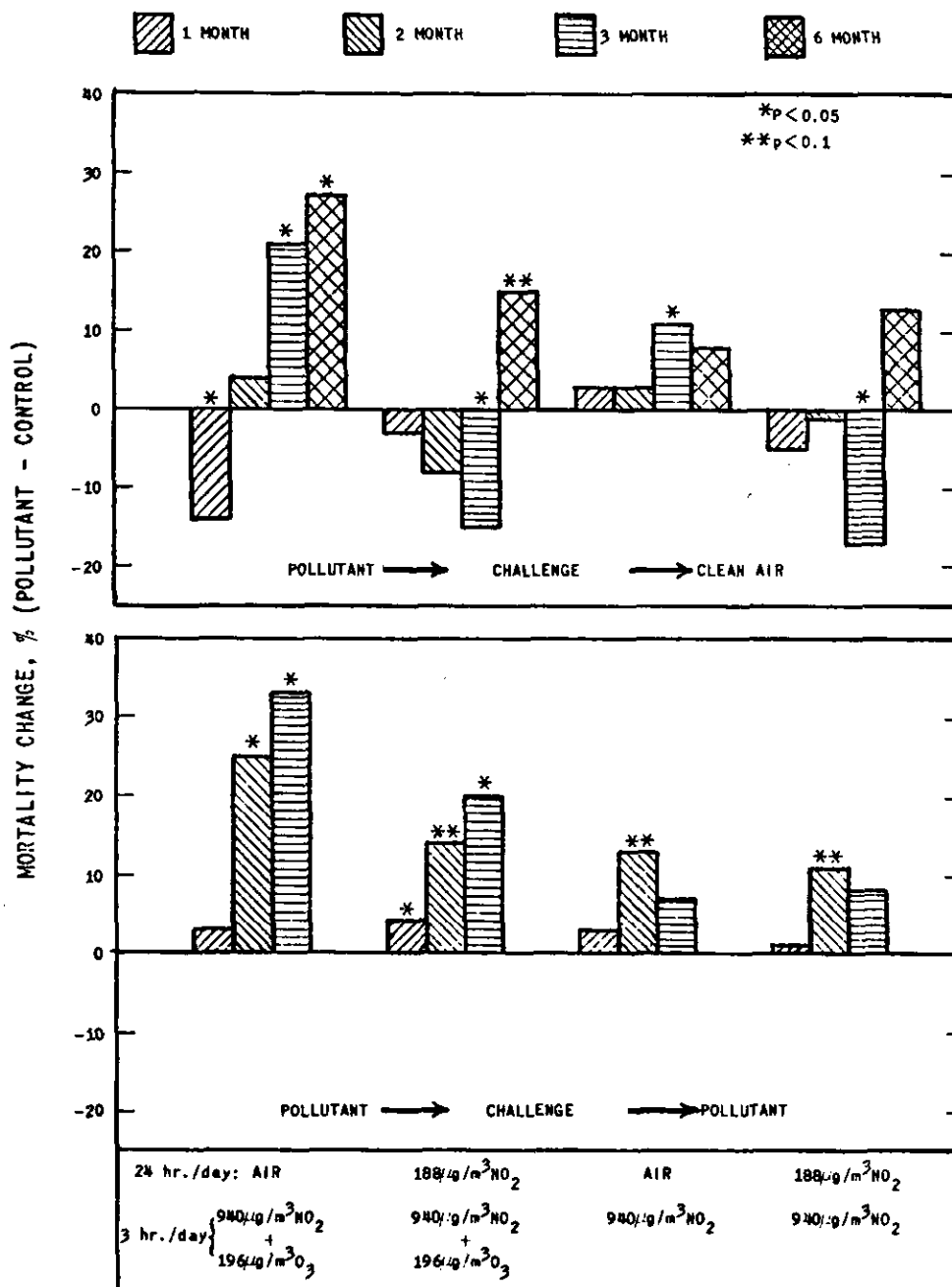

FIGURE 3. Changes in mortality from streptococcal pneumonia in mice subjected to various NO_2 and O_3 exposure regimens (6).

ity and shortened survival time (see Fig. 4) were seen in almost all exposure regimens. Moreover, these changes in resistance appeared sooner than when mice were exposed to clean air after the challenge. Another important factor appeared to be the stress of repeated daily exposure to the NO_2 and O_3 mixture. Irrespective whether or not the mice were reexposed to the pollutants or kept in clean air after the infectious challenge, increased mortality was seen in this group after 2 months or longer exposures.

The reduced mortality rates during the first 3 months of continuous exposure to 0.1 ppm NO_2 with the superimposed daily 3-hr peaks of either nitrogen dioxide and ozone mixture or 0.5 ppm NO_2 could possibly represent initial adaptation or a protective effect of the continuous exposure to nitrogen dioxide. This response occurred only after withdrawal from the polluted atmosphere and appeared to be negated by continuation of the exposure to the pollutants either for an additional 3 months or for the 14-day period after the infectious challenge.
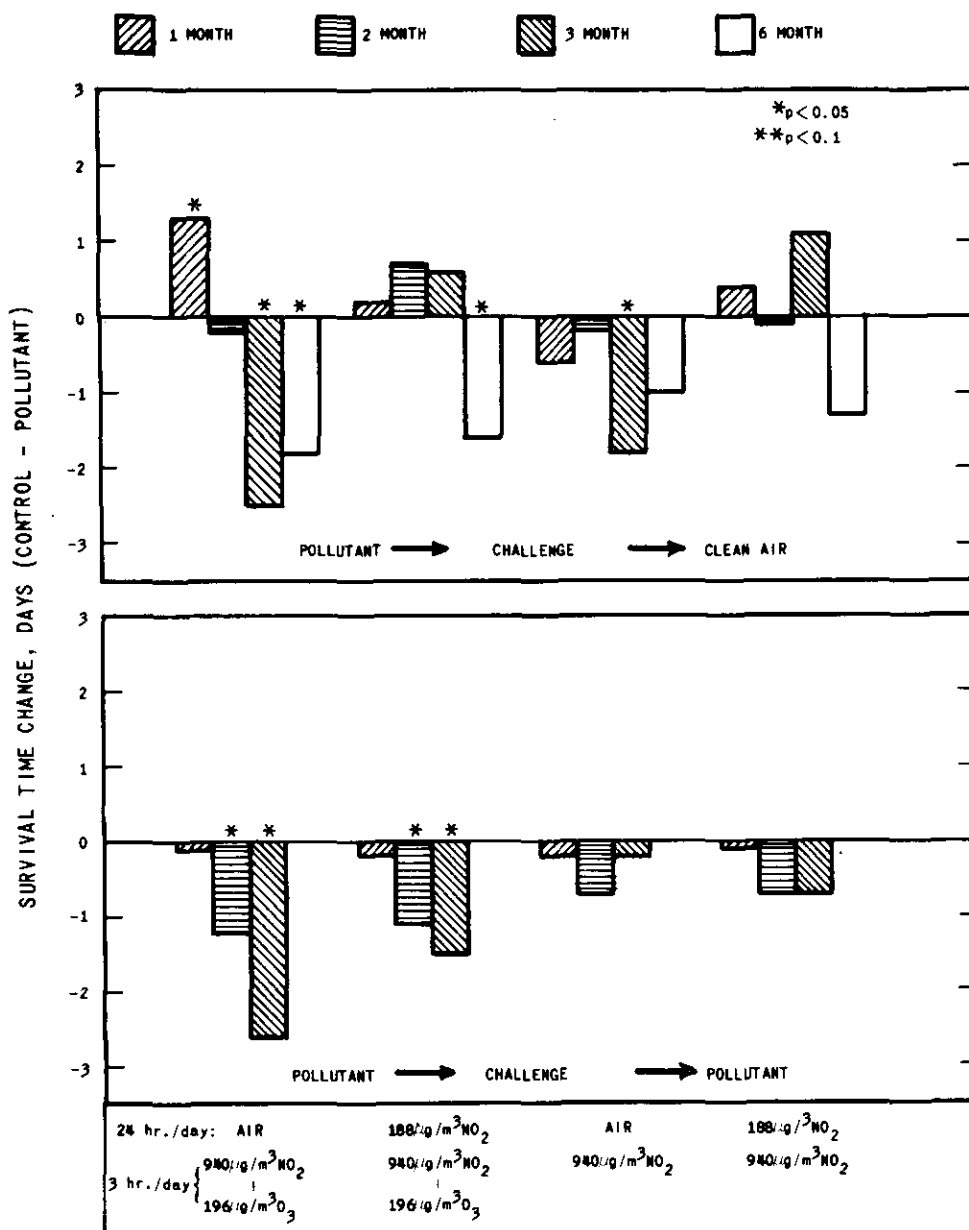

FIGURE 4. Changes in mean survival time in mice exposed to various NO_2 and O_3 regimens and challenged with Streptococcus aerosol.

Table 2. Mortality and survival time of mice exposed to 5.0 ppm (13.1 mg/m³) sulfur dioxide and challenged with Streptococcus aerosol.

SO₂ exposure	Mortality, %			Survival time, day		
	Air	SO₂	Change[a]	Air	SO₂	Change[a]
1 × 3 hr/day	24.1	26.1	+2.0	12.1	12.0	−0.1
5 × 3 hr/day	27.1	27.1	0	11.6	12.0	+0.4
10 × 3 hr/day	39.6	38.3	−1.3	10.4	10.5	+0.1
15 × 3 hr/day	31.9	30.4	−1.5	11.5	11.5	0
1 mo × 24 hr/day	9.9	7.8	−2.1	13.4	13.5	+0.1
2 mo × 24 hr/day	5.0	12.5	+7.5[b]	13.7	13.1	−0.6
3 mo × 24 hr/day	8.3	10.4	+2.1	13.4	13.3	−0.1

[a]Pollutant mortality − control mortality
[b]Significant change compared to infected mice exposed to filtered air ($p \leqslant 0.05$).

The third gaseous pollutant included in the studies was sulfur dioxide (SO₂). These experiments encompassed single and multiple 3-hr exposures as well as continuous 24 hr/day, 7 days/week exposures to 13.1 mg/m³ (5 ppm) SO₂. As seen in Table 2, exposure to SO₂ had no effect on the resistance to streptococcal pneumonia as measured by changes in mortality rates or survival time. The one statistically significant increase in mortality seen after 2 months of continuous exposure appears to be of no practical or true importance, since all the other values obtained in these exposures did not indicate any changes in resistance. Other health effect parameters measured during these studies, such as viability and phagocytic activity of macrophages, development of lung edema, body weights, rectal temperature, and SEM examination of lungs, trachea, and nasal cavities, also did not show any changes which could be ascribed to the exposure.

Effects of Particulate Pollutants

Although a considerable amount of information is now available on the effects of photochemical oxidant pollutants on the resistance to infection there is a paucity of data pertaining to the effects of particulate pollutants, especially sulfates or nitrates. The tables and figures summarize results more recently obtained in our laboratories. The results further confirm the utility of this experimental animal model system for studies of air pollutants as well as environmental contaminants of importance to occupational health.

Changes in susceptibility to streptococcal pneumonia caused by a single 3-hr exposure to zinc sulfate, zinc ammonium sulfate, and ammonium sulfate are shown in Table 3. Inhalation of 1.2 mg/m³ or more zinc sulfate or 2.1 mg/m³ or more zinc ammonium sulfate followed by a respiratory challenge

Table 3. Mortality and survival rate of mice exposed for 3 hr to sulfates and challenged with Streptococcus aerosol.[a]

SO₄, mg/m³	ZnSO₄			Zn(NH₄)₂(SO₄)₂			(NH₄)₂SO₄		
	Mortality		MST, day[c]	Mortality		MST, day[c]	Mortality		MST, day[c]
	D/T[b]	%		D/T[b]	%		D/T[b]	%	
0	373/1689	22.1	12.1	165/756	21.8	12.3	233/588	39.6	10.1
≤1.1	125/599	20.9	12.2	29/120	24.2	11.9	22/48	45.8	10.1
1.2-2.0	369/813	45.4[d]	9.1[d]	112/445	25.2	12.0	76/191	39.8	10.7
2.1-3.0	186/278	66.9[d]	6.2[d]	67/192	34.9[d]	10.9[d]	52/96	54.2[d]	9.2
3.1-4.0	—	—	—	—	—	—	47/144	32.6	11.2
≥4.1	—	—	—	45/48	93.8[d]	4.0[d]	46/110	41.8	10.3

[a]Data of Ehrlich et al. (3).
[b]Deaths per total animals (D/T).
[c]MST = mean survival time.
[d]Significant change from infected mice exposed to filtered air ($p \leqslant 0.05$).

with airborne Streptococcus resulted in significant increases in mortality and in reduced survival time in mice. Exposure to ammonium sulfate aerosol in concentrations up to 5.3 mg/m³ had no effect on susceptibility to the infection (3).

The changes in resistance to infection appeared to be related to the zinc ion present in the sulfate complex. The lesser effect of zinc ammonium sulfate relative to zinc sulfate in enhancing the severity of

the infection and the absence of any effect of ammonium sulfate could be due to the presence of the ammonium ion which could possibly neutralize the effectiveness of the metallic cation.

The data shown in Figures 5 and 6 and Table 4 appear to confirm these assumptions. Figure 5 shows the least square lines, and the corresponding 95% confidence limit resulting from linear regression analysis of excess mortalities produced by a 3-hr
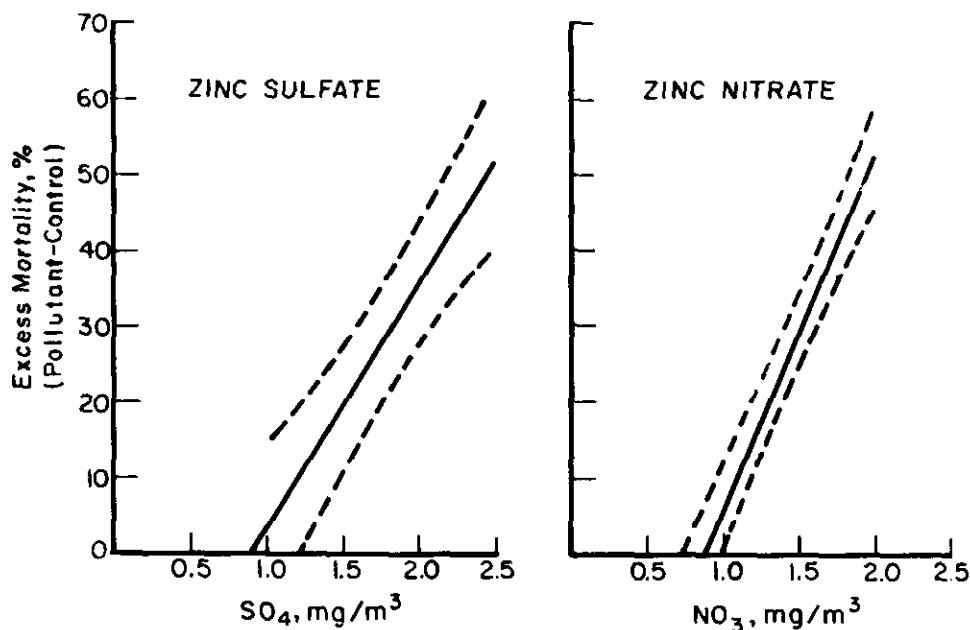
FIGURE 5. Excess mortality in mice exposed for 3 hr to zinc sulfate and zinc nitrate and challenged with Streptococcus aerosol.
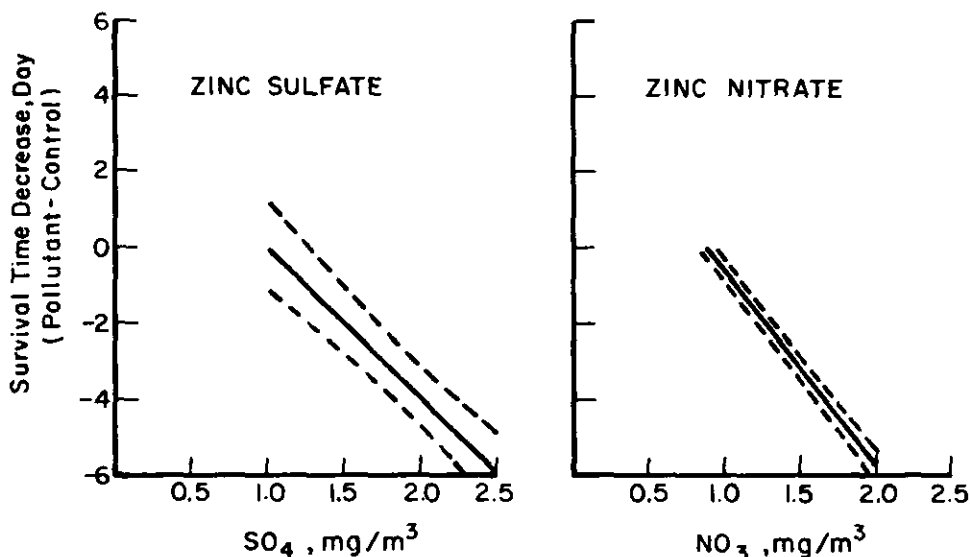
FIGURE 6. Changes in survival time of mice exposed for 3 hr to zinc sulfate and zinc nitrate and challenged with Streptococcus aerosol.

Table 4. Mortality and survival rate of mice exposed for 3 hr to sulfates and challenged with Streptococcus aerosol.

SO₄, mg/m³	$Al_2(SO_4)_3$ Mortality			MST, day	$AlNH_4(SO_4)_2$ Mortality			MST, day
	D/T	%	Change		D/T	%	Change	
0	26/192	13.5	—	12.9	19/287	6.6	—	13.4
0.8	2/47	4.3	−9.2	13.8	—	—	—	—
1.5-1.9	—	—	—	—	11/144	7.6	+1.0	13.5
2.1	18/96	18.8	+5.3	12.6	11/96	11.5	+4.9	13.2
2.5	27/48	56.3	+42.8[a]	9.2[a]	6/48	12.5	+5.9	13.0

[a]Significant change from infected mice exposed to filtered air ($p \leqslant 0.05$).

inhalation of zinc sulfate and zinc nitrate. The similarity of the dose relation of these two compounds and their effectiveness in enhancing mortality caused by the infection is clearly seen. The correlation coefficient was highly significant ($p \leqslant 0.001$) for mortality as well as the mean survival time (see Fig. 6).

The possible neutralizing effect of the ammonium ion observed in the zinc ammonium sulfate was also seen in preliminary experiments with aluminum sulfate and aluminum ammonium sulfate. As shown in Table 4, exposure to 2.5 mg/m³ of aluminum sulfate resulted in a significant increase in mortality and decrease in mean survival time. On the other hand, a similar 3-hr exposure to the same concentration of aluminum ammonium sulfate resulted in somewhat increased mortality which, however, was not statistically significant.

Figure 7 shows the relationship between the concentration of several sulfates and excess mortality. The least-square lines are based on linear regression analyses of excess mortalities resulting from a single 3-hr exposure to these compounds and infectious challenge. It is apparent from these data that cadmium sulfate was most effective and magnesium sulfate least effective in reducing the resistance to streptococcal pneumonia. The estimated concentrations of the compounds which induced 20% excess mortality (ED_{20}) were 0.2 mg/m³ cadmium sulfate, 0.6 mg/m³ copper sulfate, 1.5 mg/m³ zinc sulfate, 2.2 mg/m³ aluminum sulfate, 2.5 mg/m³ zinc ammonium sulfate, and 3.6 mg/m³ magnesium sulfate. Estimated on the same basis, exposure to 1.3 mg/m³ of zinc nitrate similarly resulted in 20% excess mortality.

Table 5 shows preliminary data on the maximum concentrations of sulfates and nitrates tested to-date which, after a 3-hr exposure, did not result in significant changes in mortality or survival time in mice challenged with Streptococcus aerosol.

The data shown in Figure 7 and Table 5 add another dimension to this animal model system. It is
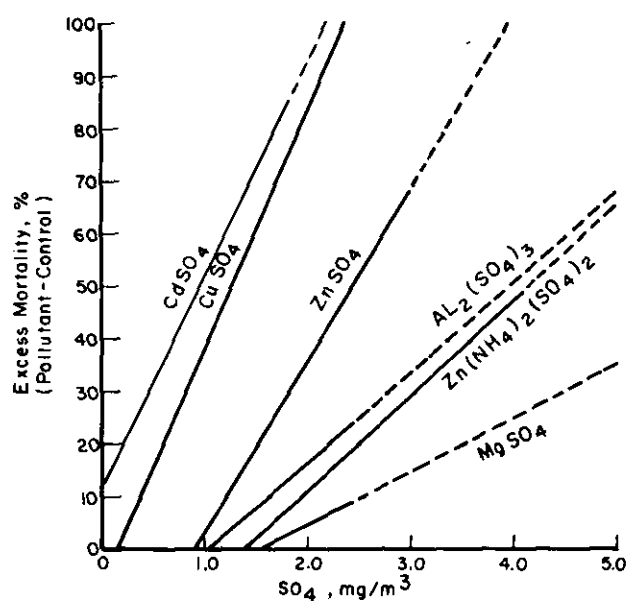

FIGURE 7. Excess mortality in mice exposed for 3 hr to sulfates and challenged with Streptococcus aerosol.

Table 5. Maximum tested concentrations of sulfates and nitrates which did not alter the resistance to streptococcal infection.

Compound	Concn, mg/m³
Aluminum ammonium sulfate, $AlNH_4(SO_4)_2$	2.4
Ferric ammonium sulfate, $Fe(NH_4)_2SO_4$	2.5
Ferric sulfate, $Fe_2(SO_4)_3$	2.9
Sodium sulfate, Na_2SO_4	4.0
Ammonium sulfate, $(NH_4)_2SO_4$	5.3
Ammonium bisulfate, NH_4HSO_4	6.7
Lead nitrate, $Pb(NO_3)_2$	2.0
Calcium nitrate, $Ca(NO_3)_2$	2.8
Sodium nitrate, $NaNO_3$	3.1
Potassium nitrate, KNO_3	4.3
Ammonium nitrate, NH_4NO_3	4.5

apparent that changes in resistance to respiratory infection can be used to rank the effects of inhalation of pollutants having a related chemical structure. In all experiments the exposure conditions, including the particle size of the aerosol, were kept identical. Thus, the differences in response can only be ascribed to the toxicity of the compounds.

Experimental Variables

Several experimental variables can affect the responses in this animal model system. They include the animal host, infectious agent, and exposure sequences.

Animals

The selection of the animal host in this model system is of a major importance. Figure 8 shows the response of mice, hamsters and squirrel monkeys exposed to nitrogen dioxide and challenged with *K. pneumoniae* aerosol (5) as the percent mortality in the three species of animals and the numbers of animals used to obtain these means. Within each animal species, the mortality data were subdivided into three groups. The first is mortality of the control group of animals challenged with the infectious agent but exposed to filtered air. The second group represents mean mortality of animals challenged with the infectious agent and exposed to concentrations of nitrogen dioxide which did not significantly enhance the mortality. The third group is the mean mortality of animals at nitrogen dioxide concentrations at which significant enhancement in mortality was observed.

The mortality of control animals indicates the range of natural resistance to bacterial pneumonia in different species of animals. The respective death rates in control mice, hamsters, and monkeys were 41%, 11%, and 0%. The respiratory dose for monkeys and hamsters was approximately 10^5 organisms, a dose of the infectious agent which repeatedly killed the Swiss albino mice. Thus, the higher concentrations of nitrogen dioxide necessary to induce a significant increase in mortality in mon-
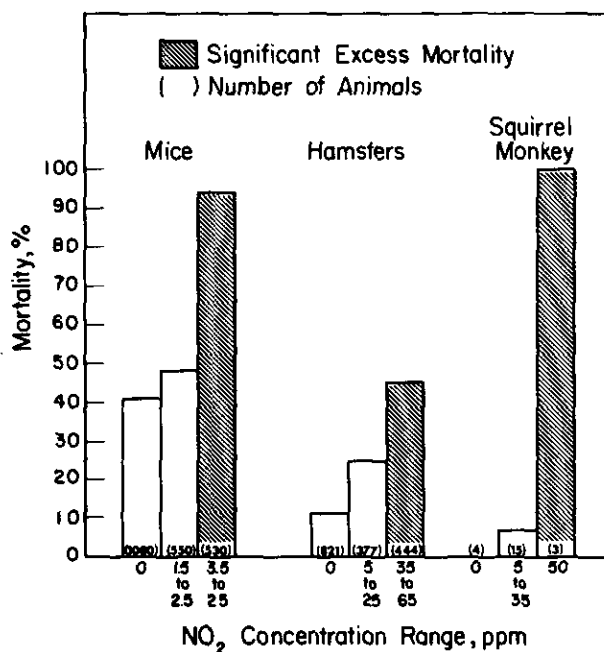

Figure 8. Effects of 2-hr acute exposure to NO_2 and challenge with *K. pneumoniae* on mortality of mice, hamsters, and squirrel monkeys (5).

keys and hamsters can, at least in part, be ascribed to their innate resistance to this infectious agent.

Differences in natural resistance to bacterial pneumonia were also seen in studies of the effects of nitrogen dioxide in four strains of mice and are shown in Table 6. The BDF mice showed significantly higher natural resistance to the infection than the other strains. However, excess mortalities ranging from 8 to 25% were observed in all four strains of mice after 3-hr exposure to 5 ppm of NO_2 and the infectious challenge.

Infectious Agent

Table 7 shows the effects of a single 2- or 3-hr exposure to nitrogen dioxide on the resistance of Swiss albino mice to bacterial pneumonia induced by inhalation of *K. pneumoniae* or *S. pyogenes* aero-

Table 6. Mortality in different mouse strains after exposure to 5 ppm NO_2 and challenge with Klebsiella aerosol.

| Strain | Air | | NO_2 | | Change |
	D/T	%	D/T	%	%
BDF (black)	31/120	25.8[a]	40/120	33.3	7.5[a]
C57BL (black)	24/70	34.3[a, b]	36/70	51.4	17.1[b, d]
Swiss (albino)	164/390	42.1[b]	262/390	67.2	25.1[c, d]
BALB (albino)	48/100	48.0[b]	72/100	72.0	24.0[c, d]

[a, b, c]Means in a column with the same superscript are not significantly different ($p \leqslant 0.05$).

[d]Significant change in mortality compared to corresponding infected mice exposed to filtered air ($p \leqslant 0.05$).

NO₂ concn		Mortality change, %[a]	
ppm	mg/m³	Klebsiella[b]	Streptococcus[c]
1.5	2.82	+10.0[d]	− 1.7
2.0	3.76	—	+14.3[e]
2.5	4.70	+ 5.7[d]	—
3.5	6.58	+54.0[e]	+28.2[e]
5.0	9.40	+48.8[e]	+35.7[e]

[a]Pollutant mortality − control mortality.
[b]2-hr exposure to NO₂.
[c]3-hr exposure to NO₂.
[d]Significant change in mortality compared to infected mice exposed to filtered air ($p \leqslant 0.1$).
[e]Significant change in mortality compared to infected mice exposed to filtered air ($p \leqslant 0.05$).

sols. A direct comparison between the two groups of results cannot be made because of the time interval separating the two studies. The work with Klebsiella was reported in 1966 (1) the one with Streptococcus in 1977 (2). Nevertheless, it is apparent that the mice were somewhat more susceptible to the Klebsiella than to the Streptococcus infection.

Exposure Sequence

The sequence and interval between the exposure to the pollutants and challenge with the infectious agent is yet another factor of importance. In all of the studies discussed previously the experimental plan required exposure to the pollutants followed within less than 1 hr by the infectious challenge. Figure 9 shows that, at least for the short-term exposures to nitrogen dioxide the extension of the interval between exposure and challenge allows a recovery

from the effects of the pollutants.

Conclusions

In discussing the importance of this animal model system in studies of health effects of air pollutants two aspects must be considered.

First is the value of the model as a highly sensitive indicator of *in vivo* effects. The changes in resistance to respiratory infection can be seen at concentrations of oxidant and other pollutants markedly lower than those detected by any other *in vivo* method. The model depicts the responses of the respiratory system and reflects the overall damage to the pulmonary defense mechanisms. Therefore, it indicates that basic defense mechanisms of the lungs have been impaired. A major part of this impairment appears to result from the damage to the alveolar macrophage system and the ensuing inability to remove the inhaled microorganisms from the lungs.

The second aspect is that this model may simulate a situation which could occur in man. Decreased resistance to respiratory infections as a consequence of exposure to air pollutants was observed in mice, hamsters and monkeys. In spite of the functional and anatomical differences of the respiratory tract and the differences in innate and acquired immunity between man and these animal species, under the proper set of circumstances man could be expected to respond to these stresses in a very similar manner. The necessary components for its occurrence in man are the presence of a sufficiently high concentration of pollutants and the presence of an infectious microorganism capable to invade and colonize in the human host exploiting the state of reduced resistance.
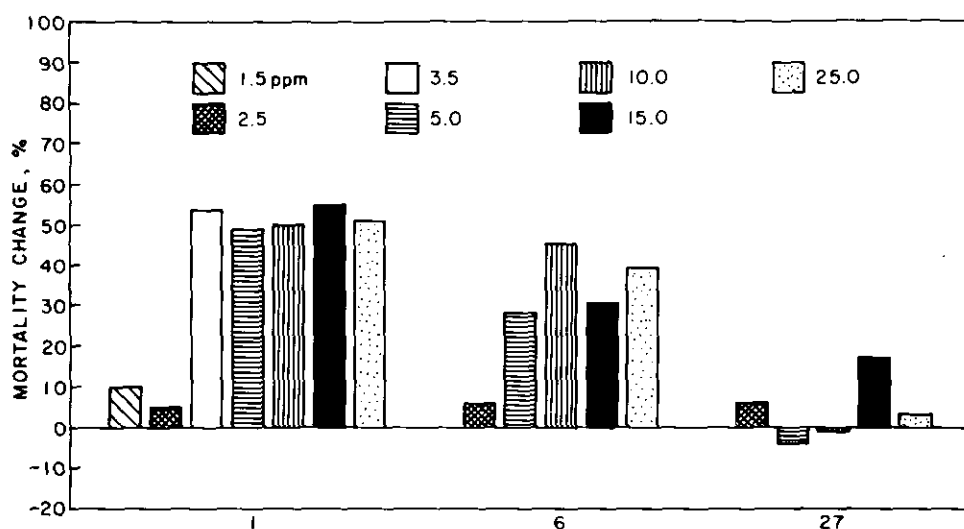

FIGURE 9. Effect of time interval between 2 hr exposure to NO₂ and infectious challenge.

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